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16. ABSTRACT

Sulfolane is a solvent which produces hypothermia and decreased oxygen consumption following acute exposure. In the present experiment, we investigated effects of sulfolane on a behavioral measure of toxicity at ambient temperatures which would either prevent or facilitate the development of hypothermia. Adult, male Long-Evans rats (N=10/dose) received a single i.p. injection of saline, 200,400 or 800 mg/kg sulfolane. Motor activity in figure-eight mazes was assessed 1 hr after dosing in testing rooms maintainted at either 20.8 C or at 32.3 C. At the warm ambient temperature, sulfolane proudced hypoactivity but not hypothermia. At the cooler temperature, sulfolane-induced hypoactivity was more pronounced, and rats were hypothermic. Therefore, a behavioral change could be detected at sublethal dosages of sulfolane in the absence of hypothermia.

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ACUTE BEHAVIORAL TOXICITY OF SULFOLANE: INFLUENCE OF HYPOTHERMIA

(Motor activity; thermoregulation; solvents)

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SUMMARY

Sulfolane is a solvent which produces hypothermia and decreased oxygen consumption following acute exposure. In the present experiment, we investigated effects of sulfolane on a behavioral measure of toxicity at ambient temperatures which would either prevent or facilitate the development of hypothermia. Adult male Long-Evans rats ($N = 10$/dose) received a single i.p. injection of saline, 200, 400 or 800 mg/kg sulfolane. Motor activity in figure-of-eight mazes was assessed 1 h after dosing in testing rooms maintained at either 20.8°C or at 32.3°C. At the warm ambient temperature, sulfolane produced hypoactivity but not hypothermia. At the cooler temperature, sulfolane-induced hypoactivity was more pronounced, and rats were hypothermic. Therefore, a behavioral change could be detected at sublethal dosages of sulfolane in the absence of hypothermia.

INTRODUCTION

Sulfolane (tetrahydrothiophene-1,1 dioxide) is a solvent which produces a rapid decrease in oxygen consumption and hypothermia following acute exposure in both rats and mice [1,2]. Sulfolane-exposed rodents maintain a normal body temperature

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and metabolic rate at an ambient temperature of 35°C, but both measures decline at cooler ambient temperatures of 15 and 25°C. Hypothermia appears to be protective against sulfolane toxicity since the LD_{50} is higher in a cool environment [2]. Furthermore, in a thermal preference test, sulfolane-exposed mice preferred to remain at the cool end of a temperature gradient [2]. To determine the influence of body temperature on another behavioral indicator of sulfolane exposure, we assessed spontaneous motor activity in rats following sulfolane exposure at ambient temperatures which would either attenuate (32°C) or facilitate (20°C) the development of hypothermia. Motor activity was chosen as a measure of spontaneous behavior in rats which is influenced by both ambient temperature [3] and core temperature [4].

MATERIALS AND METHODS

Male Long-Evans hooded rats (Charles River; Portage, MI), 60 days of age, were housed individually in cages measuring 21 × 23 × 21 cm. Animals were maintained on a 12–12 h light-dark cycle beginning at 06:00 h in an animal facility with controlled air temperature (22°C ± 2) and humidity (50% ± 10). Purina Lab Chow and water were available ad lib. On the day of dosing, independent groups of rats were introduced into the warm (32.3°C ± 0.7) or cool (20.8°C ± 0.2) testing rooms at 08:00 h, and tested between 10:00–16:00 h. Rats ($N = 10$/dose/temperature condition) received a single i.p. injection of either saline, 200, 400 or 800 mg/kg sulfolane. Sulfolane (99% pure; Aldrich Chemicals) was warmed to a fluid and dissolved in 0.9% saline in an injection volume of 1.0 ml/kg body weight.

Motor activity was assessed in figure-of-eight mazes 1 h after dosing. Activity was automatically detected during the 1-h test by 8 phototransistor/photodiode pairs which registered a count each time an infrared light beam was interrupted [5]. Immediately after testing, body temperatures were obtained using a rectal thermistor probe (Yellow Springs Instrument Co.). Body temperature, total photocell counts and the percentage of counts in the highest photocell were analyzed by separate 2-factor analyses of variance. An analysis of covariance was performed for total photocell counts using body temperature as a covariate. Analyses were conducted using BMDP-4V. Post-hoc comparisons were made using Tukey's (a) test.

RESULTS

At the cool ambient temperature, the body temperature of rats receiving 400 and 800 mg/kg sulfolane was lower than that of controls. At the warm ambient temperature, hypothermia in the rats receiving 400 and 800 mg/kg sulfolane was attenuated, if not prevented (Fig. 1). Analysis of body temperature indicated main effects of ambient temperature ($F(1,71) = 125.30$; $P < 0.00001$) and treatment ($F(3,71) = 99.58$; $P < 0.00001$), and an interaction ($F(3,71) = 19.63$; $P < 0.00001$).

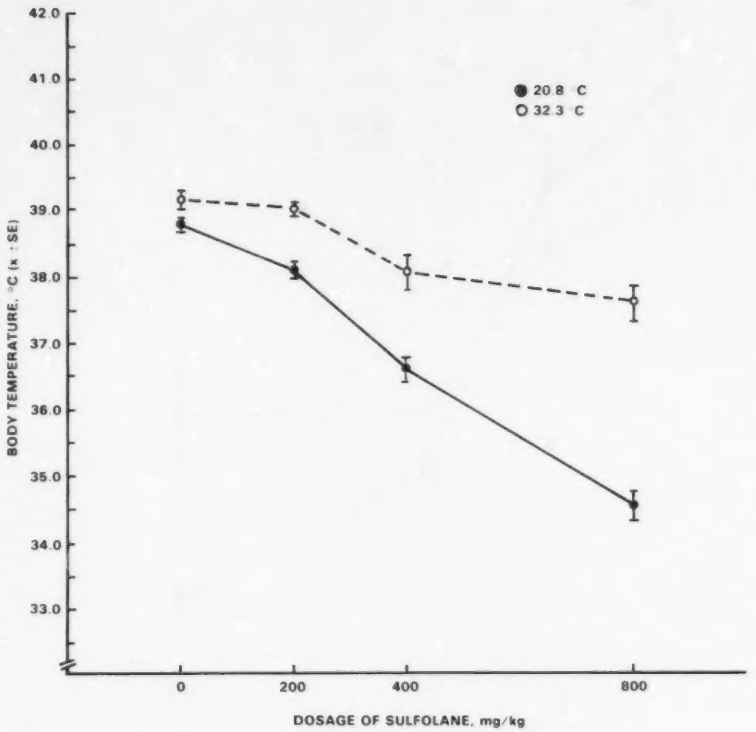

Fig. 1. Body temperature ($\bar{x} \pm$SE) for control and sulfolane-exposed rats taken immediately after activity testing at either a high (32.3°C) or low (20.8°C) ambient temperature.

One animal which received 800 mg/kg sulfolane at the warm ambient temperature died during testing.

Maze activity is shown for total photocell counts (Fig. 2) and for counts in the highest photocell as percent of total activity (Fig. 3). For total photocell counts, there was a main effect of treatment ($F(3,71) = 36.89$; $P < 0.00001$) and an ambient temperature by treatment interaction ($F(3,71) = 5.13$; $P < 0.003$). At both ambient temperatures, 400 and 800 mg/kg sulfolane produced a decrease in motor activity. When body temperature was used as a covariate in the analysis, a main effect of treatment was still evident ($F(3,70) = 5.42$; $P < 0.002$).

Analysis of the percent of total activity in the photocell recording the highest number of counts indicated main effects of ambient temperature ($F(1,71) = 40.03$; $P < 0.00001$) and treatment ($F(3,71) = 39.39$; $P < 0.00001$), and an interaction ($F(3,71) = 21.19$; $P < 0.00001$). At the cool ambient temperature, 800 mg/kg sulfolane produced a decrease in movement throught the maze by restricting activity predominantly to a singie photocell.

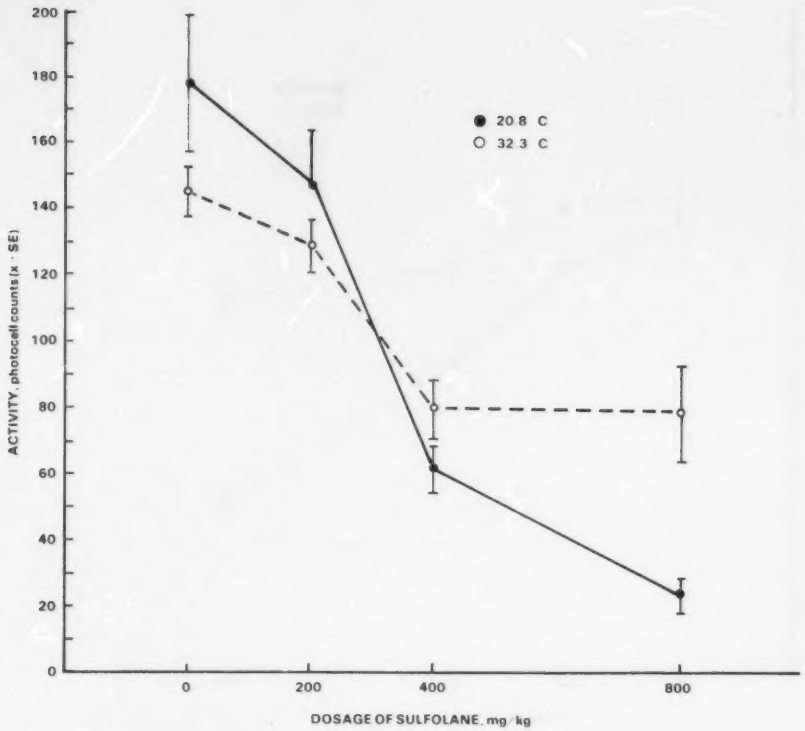

Fig. 2. Total photocell counts ($\bar{x} \pm SE$) in a figure-of-eight maze for control and sulfolane-exposed rats tested at either a high (32.3°C) or low (20.8°C) ambient temperature.

DISCUSSION

Toxicants like sulfolane, which affect thermoregulation, raise intriguing questions for the interpretation of other physiological efects. Sulfolane produced hypothermia and reductions in motor activity that were more pronounced at lower ambient and body temperatures. Although low ambient temperature has been shown to reduce lethality following sulfolane exposures and to be preferred by sulfolane-exposed mice, the acute effects of sulfolane on behavioral function were not attenuated by reducing ambient temperature. Hypoactivity produced by sulfolane exposure was still a significant treatment effect when body temperature was used as a covariate. In that sense, sulfolane reduced motor activity regardless of whether testing was conducted in a warm or cool environment. However, this reduction in activity was much greater in the cool environment (86%) than in the warm environment (45%). Clearly hypothermia contributed to the behavioral effects of 800 mg/kg sulfolane.

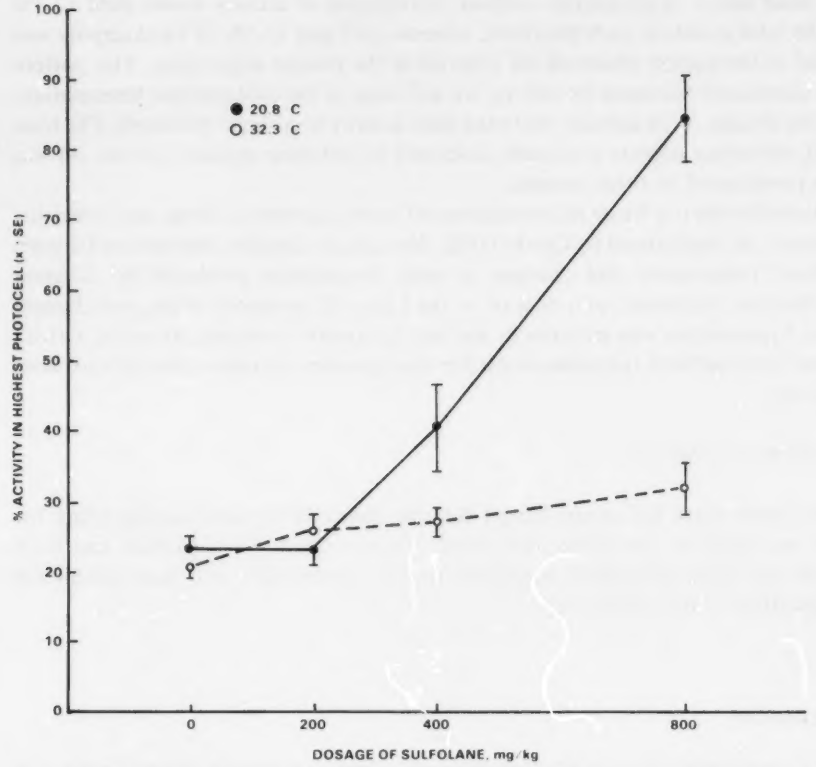

Fig. 3. Percent of total activity in the photocell registering the highest number of counts ($\bar{x} \pm$ SE) for control and sulfolane-exposed rats tested at either a high (32.3°C) or low (20.8°C) ambient temperature.

Motor activity has been shown to elevate core temperature in normal animals [4], and controls in the present experiment were slightly hyperthermic after activity testing in the warm environment. Motor activity is reduced at warm ambient temperatures in normal rats [3,6], and the activity of control rats in the present experiment was lower when tested at 32°C than at 21°C. Given the protective effects of hypothermia on the toxicity (i.e., mortality) produced by sulfolane, the decreased motor activity shown by treated animals could be a behavioral mechanism to prevent an elevation in body temperature.

Motor activity of sulfolane-exposed rats tested in the cool environment changed qualitatively as well as quantitatively. In the cool environment, the decrease in photocell counts reflected not only a reduction in activity but also a restriction of activity. In agreement with previous data [7,8], adult male rats were active throughout the maze with slightly higher activity in the figure-of-eight area than in

the blind alleys. A completely uniform distribution of activity would yield 12.5% of the total counts in each photocell, whereas 20.7 and 23.5% of total activity was found in the highest photocell for controls in the present experiment. This pattern was completely disrupted by 800 mg/kg sulfolane in the cool ambient temperature. At this dosage, 4/10 animals restricted their activity to a single photocell. The hunched, retreating posture previously described in sulfolane-exposed rodents [9] was also pronounced in these animals.

Hypothermia is a frequent consequence of acute exposure to drugs and toxicants. However, as emphasized by Gordon [10], there can be complex interactions between ambient temperature and changes in body temperature produced by different mechanisms. Sulfolane, at a dose of ¼ the LD_{50} [9], produced behavioral changes when hypothermia was minimized, and yet the greater reduction in motor activity at the lower ambient temperature further distinguishes sulfolane-exposed rats from controls.

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